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ORIGINAL RESEARCH

Oral *vs.* IV paracetamol for pain control in patients with femur fracture in the emergency department: a practical randomized controlled trial

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Abstract

Femur fracture (FF) is a common reason for admission to the Emergency Department (ED) and pain is a frequent symptom. Effective and timely pain control is essential for these patients, however, the most appropriate analgesic therapy for quick pain relief in the ED setting is not well established. This is a single-center pragmatic randomized controlled study. We have enrolled 171 consecutive patients with FF and severe pain. They were randomized 1:5 to receive treatment with paracetamol 1000 mg orally (OR) or with paracetamol 1000 mg intravenously (IV). The effect on pain relief was measured with the Visual Analogue Scale for Pain (VAS) at baseline (T0), after 1 hour (T1), 2 hours (T2), and 4 hours (T4). The primary endpoint was the reduction of pain of 1 point of the VAS at T1. This target was reached by 75% of patients treated with paracetamol IV and 44% treated with paracetamol OR ($p = 0.001$). The secondary endpoint was the reduction of pain of at least 2 points of the VAS at T4, the need for rescue therapy, and the number of adverse events. At T4 the efficacy of paracetamol IV and OR resulted in 89.5% and 88.9%, respectively ($p = 0.914$). The 17.5% of patients treated with paracetamol IV *vs.* the 3.7% treated with paracetamol OR required rescue therapy ($p = 0.082$), with prevalence among women ($p = 0.057$). No adverse effects were reported. The treatment with paracetamol 1000 mg IV and OR resulted effective and safe for patients with FF waiting for surgery. IV administration was faster in reducing pain in the first 2 hours compared to oral administration but the latter required less rescue therapy. Interestingly, our study highlighted gender differences in pain relief opening the way for a gender-tailored therapy.

Keywords

Femur fracture; Pain; Paracetamol; Emergency department; Elderly

1. Introduction

Femur fracture (FF) is a common medical emergency experienced especially by the elderly population [1]. Its incidence has been estimated to be about 9/100.000/year [2], more in women than men [3]. Trauma [4] is the most common cause of FF. Advanced age and its commonly associated conditions like osteoporosis [5] and impaired mental status [6] are important predisposing factors. FF represents a serious public health problem since it is associated with high mortality and disability risk. The overall one-year mortality rate ranges from 15% to 35% [7]. Patients aged >60 years are often admitted to the Emergency Department (ED) for FF [6], mostly presenting with leg limited function and severe pain [1, 8, 9]. The best way to detect FF is X-ray, which allows the differentiation between proximal and femoral shaft fractures [2, 10]. The management and outcomes depend on the fracture location [2, 6, 10–12]. To decrease mortality and to reduce the severity of pain, surgical treatment should be performed as soon as possible [5]. However, immediate surgery is not always possible and, the general conditions of patients could be prohibitive for immediate surgical treatment. Since pain is a feature of patients with FF, emergency physicians should ensure quick and effective pain relief directly in the ED [13]. Early and efficient pain relief can help to obtain a faster recovery of functional abilities, better preparation for surgery, a reduction in distress, delirium, cardio-pulmonary complications, and an improvement in patient quality of life.

Different therapeutic strategies have been proposed [1, 13, 14] as the multimodal approach consisting of administration of different analgesic and anesthetics drugs or femoral nerve block [1, 13–15]. However, most of these therapeutic options are often unavailable in the short term, or difficult to apply in the ED setting. Moreover, advanced analgesic techniques

can potentially trigger relevant side effects, particularly in the elderly. Literature data [16, 17] does not recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with FF due to the increased risk of a second hip fracture and antiplatelet effect. In contrast, paracetamol showed potential benefits in the early management of pain for these patients [18, 19]. Considering the lack of guidelines about the analgesic approach for patients with FF, we conducted a study to identify the most appropriate and safe analgesic therapy for elderly patients with FF in the ED before the surgical treatment.

2. Patients and methods

In this single-center pragmatic randomized controlled study, we enrolled patients aged ≥18 years admitted to the ED of Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome with FF who signed the informed consent to the study. We assessed for eligibility 210 consecutive patients. We included patients able to take analgesic therapy both orally (OR) and intravenously (IV) without allergies to the drugs administered. We excluded patients who have not signed the informed consent, patients not able to take oral treatments, patients with advanced dementia not able to express pain intensity or informed consent, patients with allergies or contraindications to paracetamol, patients with end-stage liver diseases, pregnant women, patients already taking paracetamol at home, patients with other concomitant fractures. Of 210 patients, 14 patients did not meet inclusion criteria, 12 patients declined to participate and 4 patients were excluded due to their transfer to another hospital. The remaining 180 patients were randomized 1:5 to receive treatment with paracetamol 1000 mg orally (OR) or with paracetamol 1000 mg intravenously (IV), according to our department's protocol. 150 received treatment with paracetamol IV while 30 received treatment with paracetamol OR. In the first group, 7 patients dropped out while in the group of paracetamol OR 3 patients dropped out due to their need for treatment with anesthetics drugs to place femur traction or perform sutures (Fig. 1).

Overall, 171 patients completed the study (Table 1). The Visual Analogue Scale for Pain (VAS) from 0 to 10 (with 0 = no pain and 10 = maximum pain intensity) [19] was administered at the ED admission (T0), and then, after 1 hour (T1), 2 hours (T2) and 4 hours (T4) from the administration of analgesic therapy (paracetamol 1000 mg IV for 144 patients and OR for 27 patients), according to the SUPER algorithm [20] protocol. In case of failure of the primary treatment and persistence of pain, rescue therapy with a second dose of paracetamol 1000 mg (OR-IV), or treatment with opioids (such as tramadol 100 mg IV or morphine 2–4 mg IV) was considered at T1 or T2. The administration of rescue therapy was decided by the treating physician based on the persistence at the same level or the increase in the reported pain, the presence of physiological signs of distress associated with intense pain (such as an increase in respiratory rate or heart rate, diaphoresis, and agitation).

The primary endpoint was to assess the number of patients who obtained a reduction of at least 1 point of the VAS at T1 (Fig. 2). The secondary endpoints were (a) to evaluate the number of patients who reached a pain reduction of at least 2 points of the VAS at T4 (Fig. 3); (b) to assess the number of patients who required a rescue therapy; (c) to measure the number of patients reporting adverse events for each drug treatment administered.

We collected patients' data in an SPSS V25® (IBM, Armonk, NY, USA) database. Data included demographic features, age, home medications, lifestyle habits, VAS at T0 (enrollment)-T1 (1° hour)-T2 (2° hour)-T4 (4° hour) need for rescue therapy, and allergies of all enrolled patients. Categorical variables are presented as numbers and percentages and statistically compared at univariate analysis by chi-square test, with Yates correction or Fisher exact test if appropriate. Continuous variables are presented as median (interquartile range) and compared by the Mann-Whitney U test. The significance level was set at 0.05, two-sided.

Considering that about 5% of the patients with FF could have a spontaneous pain relief of at least 1 point on the VAS score at 1 hour, and assuming that the treatment could be effective in at least 30% of the patients, given an alpha error of 0.05 (two-tailed) and a power of 80% (beta error 0.2), a total of 138 patients would be needed (23:115 with the established enrollment ratio 1:5).

3. Results

We enrolled and analyzed data of 171 consecutive patients: 125 females and 46 males mean age 81.5 (74–87) years admitted to the ED of Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome for FF confirmed with X-ray, from June 2019 to June 2020.

Patients received an initial treatment of paracetamol 1000 mg IV (144/171 patients) or paracetamol 1000 mg OR (27/171 patients) as shown in Table 1, after being randomized 1:5 according to the protocol of our department. We found that paracetamol IV was more effective than paracetamol OR in reducing pain in patients with FF in the first two hours (T2).

The primary endpoint was reached by 108 (75.0%) patients treated with paracetamol 1000 mg IV and 12 (44.4%) patients treated with paracetamol 1000 mg OR ($p = 0.001$) (Fig. 2). Stratifying the results based on gender, we found that 87 females (69.6 %) and 33 males (71.7%) reached the primary endpoint at T1 ($p = 0.007$) as shown in Table 2.

At T2 (Fig. 2), 127 patients (88.1%) treated with paracetamol 1000 mg IV reached a pain reduction of an additional point of the VAS compared to 14 patients (51.9%) treated with paracetamol 1000 mg OR ($p < 0.001$). Paracetamol 1000 mg IV was found to be more effective in decreasing pain than paracetamol 1000 mg at T2. Considering gender variation, 99 (79.2%) females and 42 (91.3%) males reached a pain reduction of an additional point of the VAS ($p = 0.0065$). In contrast, at the fourth hour (T4) the efficacy of paracetamol 1000 mg IV was the same as paracetamol 1000 mg OR. Overall, 129 patients (89.6%) treated with paracetamol 1000 mg IV had a reduction of at least 2 points of the VAS compared with 24 patients (88.9%) treated with paracetamol 1000 mg OR ($p = 0.914$) (Table 1). About this, we found that 110 female patients (88.0%) and 43 males (93.5%) reached the secondary endpoint ($p = 0.301$).

A rescue therapy (Table 1), for better pain control at T4,

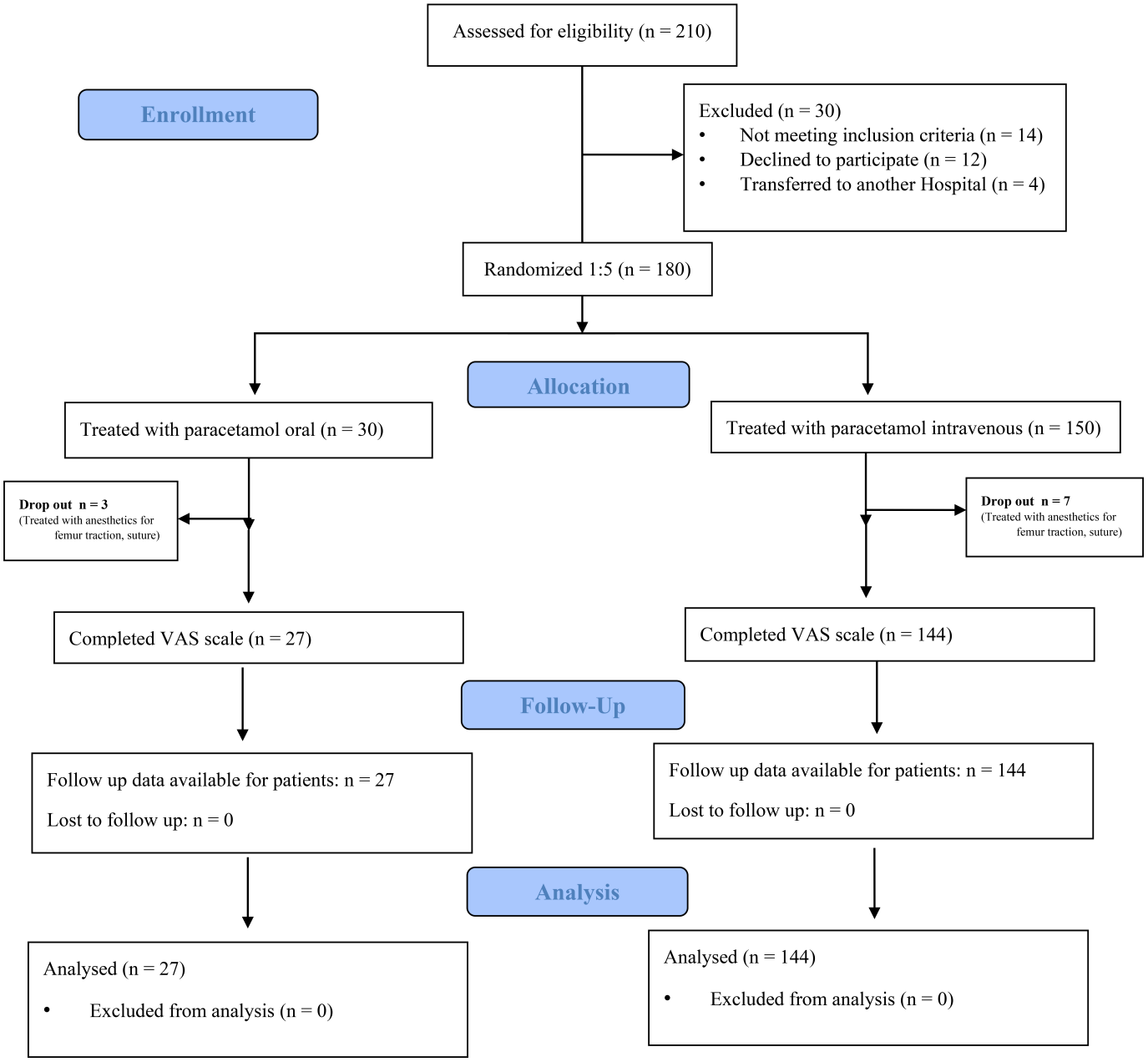

FIGURE 1. Flow diagram of enrollment, follow up, analysis of patients. VAS: Visual Analogue Scale for Pain.

TABLE 1. Characteristics of patients at baseline and endpoints.

	Total patients	Paracetamol IV n = 144	Paracetamol OR n = 27	*p* value
Age	81.5 (74–87)	81.5 (72–87)	81 (76–88)	0.569
Sex (males)	46 (26.5%)	42 (29.2%)	4 (14.8%)	0.123
LDH (U/L)	235 (197–315)	243 (197–326)	218 (190–309)	0.280
WBC ($\times 10^9$/L)	11.5 (9–17)	11 (8.4–16)	10 (9–11)	1.000
Hb (g/dL)	13 (11–15)	13 (10–15)	12 (11–14)	0.923
Primary Endpoint (T1)	120 (70.2%)	108 (75.0%)	12 (44.0%)	0.001
T2	141 (82.5%)	127 (88.2%)	14 (51.9%)	<0.001
T4	153 (89.5%)	129 (89.6%)	24 (88.9)	0.914
Rescue Therapy	26 (15.3%)	25 (17.5%)	1 (3.7%)	0.082

IV: intravenously; OR: orally; LDH: lactate dehydrogenase; WBC: white blood cells; Hb: hemoglobin.

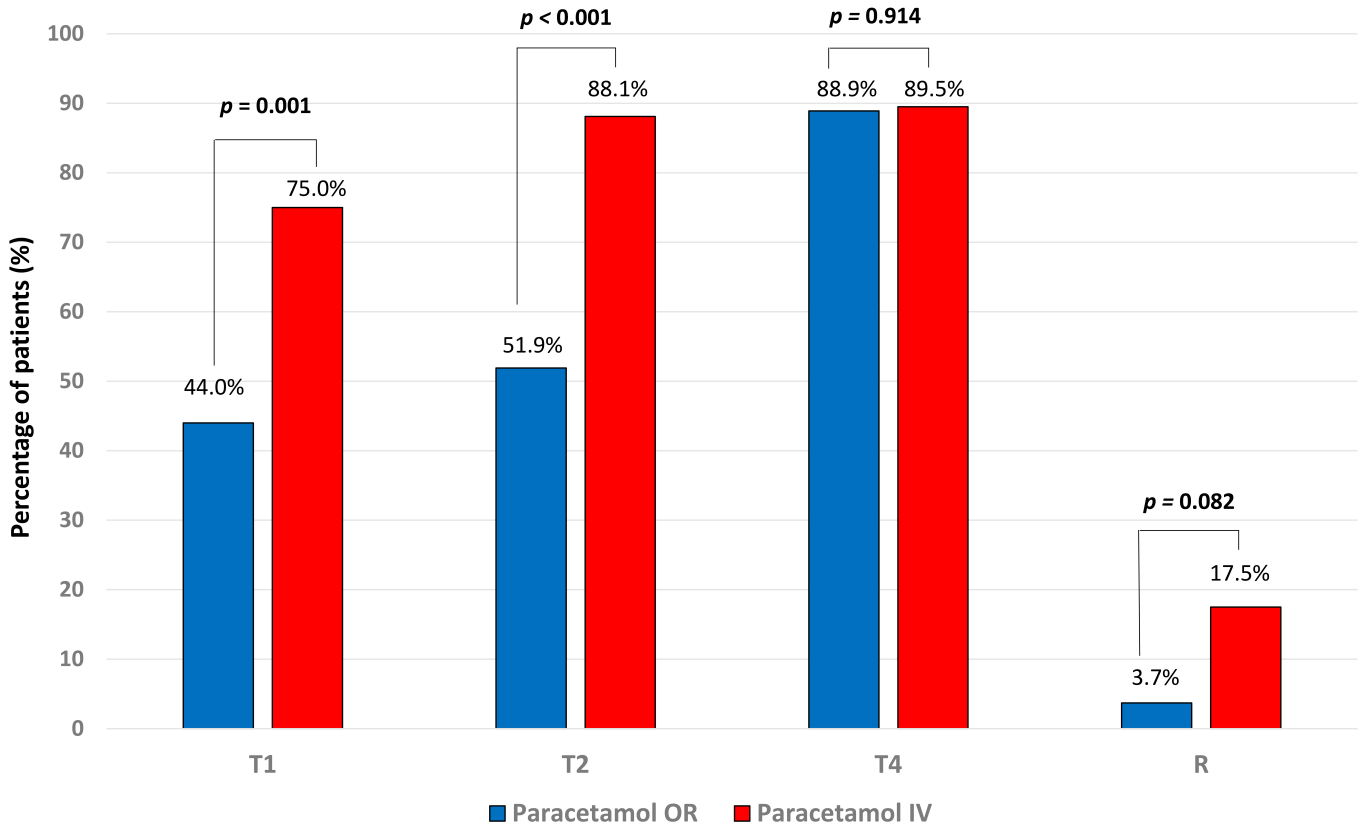

FIGURE 2. Primary endpoint, secondary endpoint, rescue therapy. Reduction of at least 1 point on Visual Analogue Scale for Pain (VAS) scale at T1, on the left; reduction of an "additional" point on VAS scale at T2; reduction of at least 2 points on VAS scale at T4; need of rescue therapy, on the right. IV: intravenously; OR: orally.

TABLE 2. Endpoints and gender variation.

	Males (n = 46)	Females (n = 125)	*p* value
Primary Endpoint (T1)	33 (71.7%)	87 (69.6%)	0.007
T2	42 (91.3%)	99 (79.2%)	0.007
T4	43 (93.5%)	110 (88.0%)	0.301
Rescue Therapy	11 (23.9%)	15 (12.0%)	0.057

was required by 25 patients (17.5%) who received paracetamol 1000 mg IV and only 1 (3.7%) patient who received paracetamol 1000 mg OR (p = 0.082). Stratifying these data by gender and route of administration, 15 female patients (12.0%) and 11 males (23.9%) treated with paracetamol 1000 mg IV needed rescue therapy (p = 0.057) (Table 2). None of the male patients treated with paracetamol 1000 mg OR required additional analgesic treatments. No adverse effects were reported within the four-hour observation time after the administration of analgesic drugs.

4. Discussion

Pain is commonly associated with FF in patients accessing the ED for this condition. Literature data show that FF occurs especially in the female population aged >80 years [2, 10, 21–23]. A systematic review of 72 studies carried out in 63 different countries revealed that Italy is among the countries with the highest incidence of hip and FF with an incidence higher than 300/100.000 inhabitants/year for women and higher than 150/100.000 inhabitants/year for men [23–25]. FF has a substantial and sometimes devastating impact on the quality of life [26], in addition to the increased mortality risk in elderly patients [27].

Emergency physicians need to provide efficient and early treatment of pain in patients with FF from admission to the ED, to improve their clinical outcomes, increase the quality of care, reduce minor and major complications, and improve patients' quality of life. Paracetamol (IV or OR) is a well-studied drug with good analgesic properties and low side effects (within a maximum dose of 4000 mg/day) [28]. It is recommended in older people instead of NSAIDs, which are responsible for an increased risk of renal failure, antiplatelet activity, gastrointestinal bleeding, and second fracture [16]. Similarly, analgesic opioids may induce relevant adverse effects in elderly patients, such as an increased risk of respiratory failure, delirium, constipation, confusion, nausea, and vomiting [29]. In our study, the administration of paracetamol 1000 mg, both IV and OR, appeared to be an effective and safe strategy in old people with pain related to FF, admitted to the ED. Within the first two hours, paracetamol 1000 mg IV produced a better and earlier pain relief compared to paracetamol 1000 mg OR. Interestingly, the analgesic activity of these two treatments became equivalent within the fourth hour. These results provide practical implications for the choice of analgesic therapy in

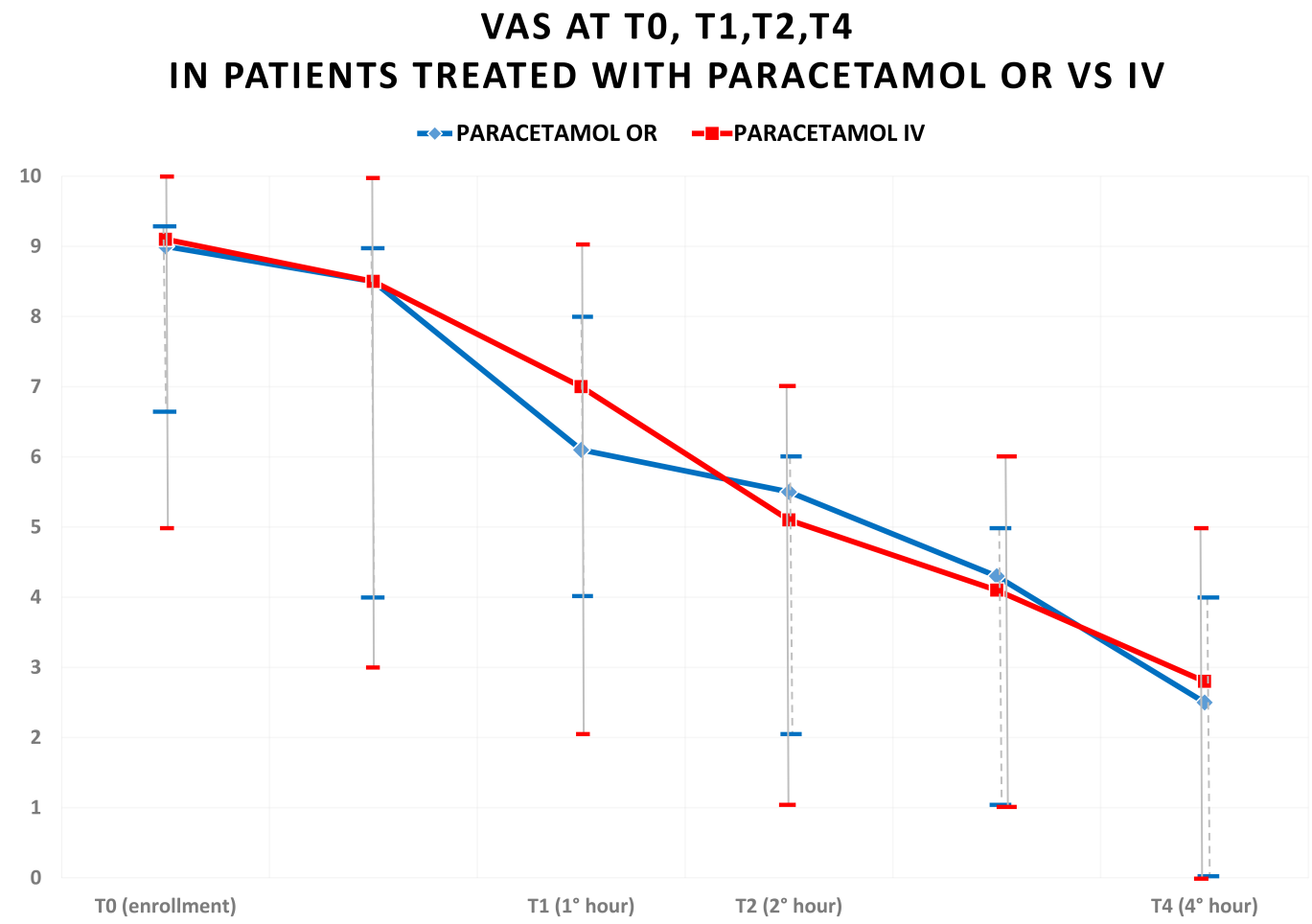

FIGURE 3. Trend of VAS. At T0 (enrollment), T1, T2, T4 in patients treated with paracetamol OR *vs.* IV. IV: intravenously; OR: orally.

the ED. Emergency physician can be confident to use the oral route for analgesic drug administration, especially when IV administration is not possible. While paracetamol OR resulted to have a slower "onset of action" than paracetamol IV, it became equivalent in the fourth hour and caused a reduced, despite non-significant, need of a rescue therapy, probably for the slightly delay in pain-response.

A very interesting result was the difference between females and males in terms of pain response to paracetamol OR. While none of the males treated with paracetamol OR required additional medical treatment for pain (from T1 to T4), a small percentage of females had persistent pain after this treatment.

These data contribute to underlining gender differences concerning pain and analgesia, highlighting the importance of a gender-tailored therapy in patients with FF [30, 31] from the admission to the ED.

Study limitations include the single-center study enrollment, the small number of patients evaluated, and the follow-up limited to 4 hours. Study strengths include the pragmatic randomized controlled design and the easy implementation in clinical practice. Nevertheless, further trials and a higher number of treated patients are required to confirm these data.

5. Conclusions

Providing an effective, safe and timely analgesic therapy in the ED for patients with FF could be a challenge for the emergency physician. The choice of an analgesic drug is influenced by several factors, especially in elderly patients, such as comorbidities, renal function, mental status, home therapy, and side effects of candidate drugs. In our study, the treatment with paracetamol 1000 mg IV and OR resulted to be effective and safe for patients with FF waiting for surgery. IV administration resulted more effective in the first 2 hours compared to oral administration but the latter required less rescue therapy. Moreover, our study highlighted gender differences in pain relief opening the way for a gender-tailored therapy. Further multicenter clinical studies are needed to validate our results including gender differences in the response to paracetamol.

ABBREVIATIONS

ED, emergency department; FF, femur fracture; IRCCS, Scientific institute for treatment and inpatient care; IV, intravenously; NSAIDs, non-steroidal anti-inflammatory drugs; OR, orally; VAS, Visual Analogue Scale for Pain.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publicly available due to privacy issues but are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

AS, FF, VO and GM—designed study. FS, ET, EF and RN—performed the data acquisition. MCo and MCa—elaborated and independently analyzed the data. AS and MP—drafted the work. FF, VO and GM—performed the critical revision of the intellectual content. SC and AS—performed the article revision. All the authors approved the final version of the article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the European Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki and it was approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome (Prot. 36041/19 ID: 2727). Only patients aged >18 years and able to give their consent have been enrolled; all patients included in the study have given their consent to participate. All the patients have given their consent to the publication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Angela Saviano, Marcello Covino and Marcello Candelli are serving as the Editorial Board members of this journal. We declare that Angela Saviano, Marcello Covino and Marcello Candelli had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GI.

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